

Chemical-Catalytic Liquid-Phase Oxidation of—

Nicotine, β -Picoline, and Quinoline to Nicotinic Acid

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EARLY in 1941 the Committee on Food and Nutrition of the National Research Council recommended the fortification of wheat flour by the addition of mineral salts and certain vitamins, one of which was nicotinic acid, the antipellagra vitamin. The estimated requirements for this purpose were 200,000 pounds of nicotinic acid per year, whereas only 10,000 pounds were made in 1940. Considering the additional requirements for medical and pharmaceutical uses, it was recently estimated that the total annual requirement for nicotinic acid approximates 600,000 pounds.

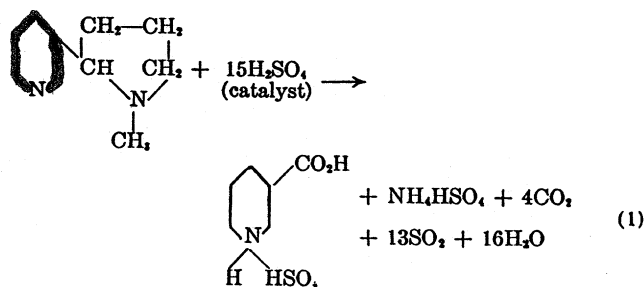
This unprecedented demand has stimulated research on a variety of starting materials from which the vitamin can be prepared, such as nicotine, β -picoline, quinoline, and pyridine. In this investigation attempts were made to develop a commercially feasible liquid-phase process for the oxidation of nicotine to nicotinic acid that would circumvent, wholly or in part, certain disadvantages of previously known methods.

Good yields of nicotinic acid have been obtained by the partial oxidation of nicotine with chemical oxidizing agents, such as nitric acid (10), potassium permanganate (4), and potassium dichromate (3). Although the last two are suitable for laboratory experiments, their cost is high for use on a commercial basis. The nitric acid method has been employed to some extent in industry, but the time required for the reaction, the quantities of strategically important oxidizing agent necessary, and the inherent explosive hazard are disadvantageous.

In view of the successful oxidation of naphthalene to phthalic anhydride with sulfuric acid in the presence of catalytic agents

A new chemical-catalytic procedure has been developed for the oxidation of nicotine, β -picoline, and quinoline to nicotinic acid. The maximum nicotinic acid yield from β -picoline approximated 50% of the theoretical, and that from both nicotine and quinoline was about 75% of theoretical. This method of oxidation represents an improvement in some respects over previously known procedures, although the high reaction temperature is a disadvantage. It is believed that selenium contamination can be satisfactorily minimized or even eliminated.

(6, 8), it appeared possible that the desired partial oxidation of nicotine could be accomplished with sulfuric acid according to the equation:



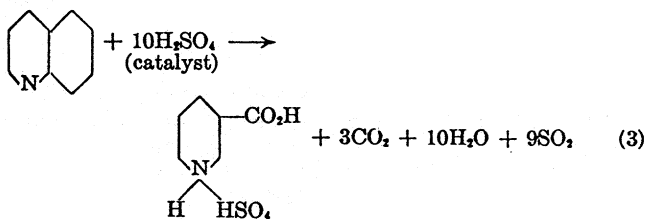
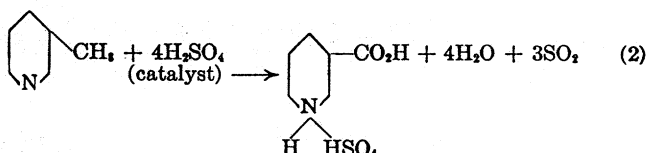
Attempts to oxidize nicotine to nicotinic acid bisulfate with sulfuric acid in the absence of an oxidation catalyst resulted in low yields of the desired product, since most of the nicotine was converted into sulfur-containing tarry derivatives. The yields of nicotinic acid bisulfate were substantially increased, however, when certain oxidation catalysts were included in the reaction mixture. Mercuric sulfate (8) and bismuth trinitrate (6), which have been employed as catalysts in the sulfuric acid oxidation of

naphthalene, were found to be moderately effective in the sulfuric acid oxidation of nicotine. Selenium, selenium dioxide, and copper selenite were much more effective.

Although selenium (1, 5, 7, 10) and copper selenite (11) have been employed as catalysts in the Kjeldahl nitrogen determination, the use of these and similar catalytic agents has not been previously reported for the partial oxidation of nicotine. An investigation by Sreenivasan and Sadasivan (9) of the action of selenium in the Kjeldahl analysis indicated that the increased oxidation rate was achieved by a rapid and reversible reaction system of the type $\text{Se} \rightleftharpoons \text{SeO}_2$ in the absence of mercuric oxide and another of the type $\text{SeO}_2 \rightleftharpoons \text{SeO}_3$ when mercuric oxide was present. It appears that these conclusions afford an explanation for the observations disclosed here.

The effectiveness of selenium as catalyst for the sulfuric acid oxidation of hydrogen, ethylene, and carbon monoxide at 237° C. was reported previously (7). Since palladium surpasses selenium in catalytic activity in the oxidation of hydrogen and carbon monoxide, it is possible that the former might be a more effective catalyst in the sulfuric acid oxidation of nicotine, β -picoline, and quinoline to nicotinic acid.

Although this laboratory is concerned primarily with utilization of the tobacco product nicotine, it was thought desirable to include β -picoline and quinoline for comparison. A number of experiments indicated that this oxidation method is also applicable to these coal tar bases according to Equations 2 and 3:



CATALYTIC OXIDATION

The general procedure for the catalytic liquid-phase oxidation of nicotine involved heating a stirred mixture of catalyst, nicotine, and sulfuric acid in a three-neck reaction flask equipped with a thermometer, a mercury-sealed stirrer, and a goose-neck column connected to a downward condenser that discharged into an ice-cooled graduated cylinder. The weight of sulfuric acid added to the reaction mixture was slightly in excess of the amount required according to Equation 1. Although some oxidation of nicotine took place at about 200° C., as indicated by a slight evolution of gaseous products, the reaction was usually carried out at 250° to 330° C. Above 250° C. the reaction proceeded at a moderate rate, accompanied by evolution of carbon dioxide, sulfur dioxide, and water. Water was removed to prevent dilution of the sulfuric acid; the quantity evolved indicated the extent of oxidation. Heating was discontinued when approximately the theoretical amount of water had distilled into the graduated cylinder. This quantity included the amount of water present in the 95% sulfuric acid as well as that formed in accordance with Equation 1.

The reaction mixture was then diluted with about five volumes of water, the catalyst filtered, and the filtrate neutralized with sodium hydroxide solution. The neutral mixture was then clarified by boiling with activated carbon. After removal of the decolorizing material by filtration, the clear filtrate was adjusted to a pH of 2.5 to 2.9, and a slight excess of cupric acetate in aqueous solution was added. Several hours of standing at room

temperature were usually required for complete precipitation of the cupric nicotinate. It was found that the purity of this copper salt was dependent upon the pH of the supernatant liquid, and that the salt was essentially pure only when the pH of the solution was within the range of about 3.6–3.9 after copper nicotinate precipitation. Whenever this pH range was adjusted, the solution was allowed to stand for an additional 30 minutes prior to filtration of the copper nicotinate.

The oxidation yield was calculated from the isolated amount of copper nicotinate dried to constant weight at 110° C. Virtually a quantitative yield of nicotinic acid was obtained by treatment of an aqueous suspension of the cupric salt with an excess of hydrogen sulfide. The nicotinic acid was recovered by concentration of the aqueous filtrate after removal of the copper sulfide by filtration. The acid thus obtained from oxidation experiments 24, 32, and 40 contained 2.2, 1.2, and 2.7 parts per million of selenium, respectively, after one recrystallization from water.

The theoretical quantities of sulfuric acid required to oxidize β -picoline and quinoline to nicotinic acid bisulfate, carbon dioxide, and water are less than that required for an equivalent molar quantity of nicotine. This allowance for the amount of sulfuric acid in the oxidation mixtures was the only significant modification required for adaptation of the liquid-phase oxidation process to β -picoline and quinoline.

NICOTINIC ACID YIELDS

The test conditions for the catalytic liquid-phase oxidations of nicotine, β -picoline, and quinoline are summarized in Table I. In experiments 1 and 2 the oxidation of nicotine was conducted in the absence of a catalyst, with the result that only an 18.9–22.4% yield of copper nicotinate was obtained. The major portion of the oxidation products was a sulfur-containing tar that precipitated during neutralization of the reaction mixture. In subsequent oxidations this tar formation was substantially decreased and in some cases completely eliminated by inclusion of a catalytic agent in the oxidation mixture.

Experiments 3 to 7, inclusive, were made to correlate the amount of distillate removed from the reaction mixture with the yield of nicotinic acid. The maximum yield in this series was obtained by the removal of 89 ml. of distillate, which corresponds closely to the calculated sum of water originally present in the sulfuric acid and that formed according to Equation 1 (91.1 ml.). However, in consideration of the possible retention of water by the slight excess of sulfuric acid, the competing sulfonation and oxidation reactions, and the discrepancy between actual and theoretical yields, it appears that the volume of distillate evolved should be used only as an approximate indication of optimum conditions.

The variations in yield of nicotinic acid obtained in experiments 5, 8, and 11 indicate that the quantity of mercuric sulfate catalyst is influential, but this is not substantiated by the experimental data obtained with other catalysts. When experiment 9 is considered along with 5, 8, and 11, there appears to be no well-defined trend.

In experiment 10 the increased reaction time, necessitated by the larger quantities of reactants, did not produce a yield appreciably different from that of experiment 5.

Although bismuth has been reported to be superior to mercury as a catalyst in the sulfuric acid oxidation of naphthalene to phthalic acid anhydride, bismuth trinitrate was not so effective as mercuric sulfate in catalyzing the oxidation under investigation. With bismuth trinitrate as a catalyst, the reaction proceeded more slowly, and a higher temperature was required to remove approximately the theoretical quantity of distillate. The maximum yield obtained with the bismuth trinitrate catalyst was 34.4% (experiment 12), which is inferior to the highest yield, 46.4%, from the mercuric sulfate catalyzed oxidation (experiment 11).

TABLE I. CATALYTIC LIQUID-PHASE OXIDATION OF NICOTINE, β -PICOLINE, AND QUINOLINE

Expt. No.	Organic Base, Grams	95% H ₂ SO ₄ , Grams	Catalyst, Grams	Reaction Temp., °C.	Total Time of Heating ^b , Min.	Reaction Time ^c , Min.	Dist., Ml.	NaOH to Neutralize Reaction Mixture, G.	Copper Grams	Nicotinate Cu content, %	Yield % of theoretical
Nicotine											
1	40	405	None	298-317	79	70	91	94.5	7.2	20.82	18.9
2	40.5	368	None	280-320 ^a	70	60	80	...	8.6	20.53	22.4
3	40	405	HgSO ₄ , 25	257-303	38	25	84	102	10.85	20.60	28.6
4	40	405	HgSO ₄ , 25	260-302	41	27	86.5	103	11.00	20.70	29.0
5	40	405	HgSO ₄ , 25	252-303	48	33	89	89	12.70	20.84	33.4
6	40	405	HgSO ₄ , 25	258-303	51	38	94	73.5	10.00	20.74	26.3
7	40	405	HgSO ₄ , 25	257-301	57	45	98	57.5	9.20	20.76	24.2
8	40	405	HgSO ₄ , 15	240-304	37	27	88	90	9.90	20.06	26.0
9	40	405	HgSO ₄ , 35	259-302	52	43	87	72	7.30	20.29	19.2
10	200	2025	HgSO ₄ , 125	264-308	112	81	410	342	60.7	21.00	32.0
11	40.5	552	HgSO ₄ , 30	265-295	80	70	72	225	17.8	21.26	46.4
12	40	405	Bi(NO ₃) ₃ ·5H ₂ O, 25	280-315	84	74	84	120	13.1	20.67	34.4
13	40.5	368	CuSeO ₄ ·2H ₂ O, 5 + HgSO ₄ , 5	255-325	74	64	89	38	18.2	20.88	47.4
14	40.5	405	Se, 2 + HgSO ₄ , 2	264-310	39	31	86	53	17.6	20.73	46.4
15	40	405	Se, 2 + V ₂ O ₅ , 2	260-305	36	29	86	22.7	22.7	20.27	59.7
16	40.5	415	CuSeO ₄ ·2H ₂ O, 5	247-310	114	105	80	120	15.0	...	39.1
17	40.5	386.5 + 30 g. H ₂ O	SeO ₂ , 20	230-275	235	225	108	75	24.6	20.94	63.9
18	40	405	Se, 2	270-313	45	37	88	67.3	10.6	20.48	27.9
19	40	405	Se, 4	267-308	39	31	86	38.7	20.5	20.76	54.0
20	40	405	Se, 15	245-304	48	39	88	46.2	24.2	20.55	63.6
21	40	405	Se, 15	259-309	52	40	88	46.2	20.7	20.73	54.5
22	40	405	Se, 30	258-310	56	42	88	42	22.1	20.66	58.1
23	40	405	Se, 40	257-305	54	41	90	44.2	20.4	20.69	53.7
24	40.5	405	Se, 40	260-305	69	60	91	43.0	29.4	21.25	76.6
β -Picoline											
25	26	138	HgSO ₄ , 15	310-320	57	45	26	72	16.4	20.18	38.1
26	93	434	Se, 4	280-353	86	77	82	113	65.1	21.00	42.3
27	93	434	Se, 2 + V ₂ O ₅ , 2	262-330	118	100	72	169	36.9	20.93	48.0
28	93	434	Se, 10	281-309	78	68	56	199	68.6	20.46	44.6
29	93	434	Se, 20	278-304	79	67	49	201	67.8	20.43	44.0
30	93	434	Se, 30	275-307	80	69	54	189	73.2	20.57	47.5
31	93	434	Se, 40	275-308	78	68	54	195	72.6	20.64	47.2
32	93	434	Se, 30	262-310	312	299	71	129	79.2	21.17	51.5
Quinoline											
33	43	360.6	Se, 4	278-310	39	31	76	48.5	29.1	21.04	57.0
34	43	360.6	Se, 2 + V ₂ O ₅ , 2	265-320	37	29	76	49.0	25.5	21.09	50.0
35	43	361	Se, 10	269-307	38	31	76	52.5	31.2	20.78	61.0
36	43	361	Se, 20	240-305	45	37	76	53	31.2	21.03	61.0
37	43	361	Se, 30	252-306	45	38	76	53	30.9	21.04	60.5
38	43	361	Se, 40	255-306	45	38	76	46	30.1	20.7	59.0
39	43	361	Se, 30	245-310	47	38	74	47.2	33.7	21.06	66.2
40	32.25	294.5	Se, 25	255-310	39	30	58	64	28.6	20.96	74.5

^a Temperature on obtaining first drop of distillate to maximum temperature employed.^b Time elapsed in heating from room temperature to discontinuation of heating.^c Time elapsed between obtaining first drop of distillate and discontinuation of heating.^d Calculated, 20.67%.^e Approximate

The use of mixed catalysts in experiments 13, 14, and 15 resulted in nicotinic acid yields that compared favorably with the maximum yield obtained with mercuric sulfate. These runs were prompted by the results obtained with similar mixed catalysts in the Kjeldahl procedure (1, 2, 5, 7).

Experiments 18 to 24, inclusive, were designed to determine the influence of the amount of metallic selenium catalyst upon the yields of the desired product. When the ratio of selenium to nicotine by weight was at least 0.10, there was no well-defined correlation between nicotinic acid yields and the quantity of catalyst used. It appears that the lower limit of selenium required for good yields of nicotinic acid is approximately one tenth of the weight of nicotine to be oxidized. This is a probable explanation for the low yield obtained in experiment 16, in which 5 grams of copper selenite dihydrate (equivalent to only 1.74 grams of selenium, or a ratio of 0.04) was employed as a catalyst.

The sulfuric acid was diluted in experiment 17 in order to facilitate control of the preliminary oxidation at about 250° C. The longer reaction time at a temperature lower than that generally employed did not appreciably affect the yield of nicotinic acid.

Of the numerous experiments performed in this study, experiment 24 produced the highest yield of nicotinic acid (76.6% of the theoretical amount) from nicotine. In general, the best yields were obtained when the alkali required to neutralize the reaction mixture approximated the calculated quantity on the basis of excess sulfuric acid and acid sulfate salts. This was to be anticipated, since an abnormally high alkali consumption indicates sulfonation in addition to oxidation.

The best experimental conditions for the catalytic sulfuric acid oxidation of nicotine were applied to β -picoline and quinoline as indicated in Table I. In general, the oxidation of β -picoline was much more sluggish than that of quinoline and produced a lower yield (percentage of theoretical) of nicotinic acid. Since quinoline may be oxidized to quinolinic acid, which undergoes decarboxylation to nicotinic acid at elevated temperatures, it is probable that quinolinic acid is an intermediate in Equation 3.

In this investigation the yields of nicotinic acid were not markedly altered by variations in sulfuric acid strength or by conducting the reaction under reduced pressure.

ACKNOWLEDGMENT

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